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INVITED COMMENTARY

Relationship between IGF-I and skeletal aging

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With advancing age, bone mass steadily declines. Between early adulthood and old age, women lose about 50% of their cancellous bone and 30% of their cortical bone, and men lose about 30% and 20% respectively. At the same time, there is a progressive decline in the circulating and skeletal concentrations of insulin-like growth factor-I (IGF-I). Expectations are high that the continuous decline in IGF-I activity with age may be a major, and potentially preventable, cause of skeletal aging.

Indeed, there is convincing evidence for a role for IGF-I as an osteotropic agent: it is present in large amounts in human skeletal tissue. Numerous *in vitro* and animal studies have demonstrated anabolic effects of IGF-I on bone cell metabolism (1). Positive associations between circulating IGF-I or related parameters and bone mineral density (BMD) have been reported for both normal individuals and patients with osteoporosis (2). Additional support for an anabolic skeletal function of IGF-I comes from patients with a deficiency or excess of growth hormone (GH). Bone mass and circulating IGF-I concentrations are both lower than normal in GH deficiency of childhood and young adult onset and can be, at least in part, restored by GH replacement. Correspondingly, patients with GH excess tend to have a higher than normal bone density (3).

In view of these data, the results of the study by Janssen *et al.* (4) in this issue of the *European Journal of Endocrinology* must be disappointing. Analyzing circulating free and total IGF-I concentrations in a large population-based sample of 55–80-year-old men and women, these authors barely observed a positive relationship between circulating IGF-I and BMD in men, and no relationship at all in women. However, sobering as these data are, they are fully in line with the weak or missing associations between circulating IGF components and BMD in the few other population-based studies that have been reported so far (5–7). Population-based studies are the best option to guard against confounding bias, such as nutrition or physical fitness. This may be one of the reasons why the relationship between IGF-I and BMD is much weaker than that reported in several studies with more selected patients.

There are various explanations for the weak performance of circulating IGF-I as a determinant of human bone mass in old age. First, the impact of IGF-I on adult bone may indeed be modest. BMD in adults who have acquired GH deficiency after full skeletal maturation is only 0.5-1 standard deviations below that of age-matched controls, and there is no evidence for a progressive bone loss with time (3). One reason for the seemingly larger impact of IGF-I during childhood and adolescence may be a gradual blunting of the anabolic effect of IGF-I on bone with age. IGF-I stimulates both bone formation and bone resorption, and the proportion between the two might change as a function of age. *In vitro* studies have suggested that human osteoblasts are less responsive to IGF-I in old age (8). It is as yet unclear whether this is balanced by a similar decline in the responsiveness of osteoclastic cells. Even the weak association between circulating IGF-I and bone mass in the elderly may be reminiscent of the beneficial effects of IGF-I on peak bone mass, as individual differences in IGF-I activity may persist throughout life. Compatible with such an hypothesis of a waning anabolic effect of IGF-I on bone, circulating IGF parameters in the 50–80-year-old men and women from the Heidelberg cohort of the European Vertebral Osteoporosis Study study were weakly positively correlated with baseline BMD values (5), but not with longitudinal changes in BMD over a 2–3 year observation period (11).

However, there are many pitfalls that may result in an underestimation of the true impact of IGF-I on skeletal aging. One of the most critical issues is whether circulating IGF-I concentrations are representative of skeletal IGF-I concentrations. It is conceivable that skeletal IGF-I activity differs greatly from that of circulating IGF-I because of the complex IGF regulatory system in bone tissue. In fact, data from our laboratory suggest that, despite age-associated decreases in both human cancellous bone matrix and serum, IGF-I concentrations between the two compartments hardly correlate with each other at all (11). Of possibly even greater significance, only bone matrix IGF-I was significantly associated with trabecular bone volume in these samples, indicating that measuring circulating IGF-I levels may underestimate the impact of IGF-I on bone metabolism.

It is also important to distinguish between the role of IGF-I in the decline of bone mass with age *per se* and its role as a determinant of the *variability* in this decline, because these may be two different issues. The relative decrease in IGF-I activity in old age, particularly in

combination with a lower responsiveness of the osteoblasts, may contribute to the reduced bone-forming capacity. It may thus be essential for the negative bone balance at the level of the remodeling unit. On the other hand, there is reason to believe that IGF-I is only one of many components that determine the variability of age-associated bone loss. Other factors with an equally strong functional relevance for bone mass, but a more variable expression, may play a far greater role in determining the individual rate of age-associated bone loss. This is best exemplified by the relationship between bone mass and bone turnover in old age. With IGF-I a major determinant of bone turnover in old age, one would expect a decline in the rate of bone turnover. In contrast, the rate of bone turnover is rather accelerated in elderly women, even many years after menopause. In fact, the individual rate of bone turnover becomes a progressively stronger negative determinant of bone mass with advancing age (9). As these age-related increases in bone turnover are probably less pronounced in men, this may be one of the reasons why gender-specific differences in the relationship between IGF-I and BMD were observed in the present study by Janssen *et al.* (4).

Many of the problems inherent to observational studies are circumvented by interventional studies. In a recent study, Holloway *et al.* (10) administered GH in a cyclical pattern to postmenopausal women for 2 years at a dose that restored circulating IGF-I concentrations to those of young adults. Interestingly, this resulted in a slight increase in BMD at the lumbar spine and selected areas of the femoral neck. Admittedly, the increases in BMD in this study were subtle and may not necessarily have been due to IGF-I-dependent effects of GH. Nevertheless, if it is confirmed that raising IGF-I concentrations has a sustained positive effect on bone balance, this will be a strong argument for the functional relevance of the IGF-I system in age-related bone loss.

In summary, there is no good evidence that circulating IGF-I is a useful indicator of bone mass or bone loss in the elderly. A better understanding of the local skeletal IGF system is necessary to clarify whether it may be a stronger determinant of age-associated bone loss. We also need more longitudinal studies to find out the long-term effects of 'rejuvenating' IGF-I concentrations on bone mass in elderly individuals. The newer orally active GH-releasing peptides could be of great help in this respect. Our efforts to understand the relationship between IGF-I and skeletal aging have come of age themselves, but defining the place of IGF-I in skeletal aging remains a continuing challenge.

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